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Thimerosal VSD study

Phase I

Update

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Following is an update on the proceedings and findings so far of the first phase of this proposed two phased study. I have used the original protocol as outline for this update.

Study design:

Retrospective cohort study using the Vaccine Safety Datalink (VSD) automated data.

Eligibility criteria:

Eligibility was restricted to children who meet the following criteria:

1. Born in 1992 or later.
2. Eligible HMO member since birth (i.e. "born into the HMO").
3. Continuously enrolled until the first birthday

The following children were excluded from the analyses:

- Premature and severe premature children. Prematurity was defined as birthweight of 1000-2499 grams or gestational age of 28 - 37 completed weeks. Severe prematurity was defined as birthweight of less than 1000 g or less than 28 completed weeks. We identified these children by the ICD9 code 765.
- Children that did not receive two polio vaccines by the age of 1. This condition was set to avoid including children enrolled in the HMO that did not use the services. Polio was considered the most commonly accepted vaccination.
- Children that received hepatitis B immunoglobulin, as these were more likely to have higher exposure and outcome levels.
- Children that had the diagnosis before the age at which the exposure was assessed.
- Children in whom any major congenital or perinatal problem occurred (including any unspecified problem involving the cardiac, respiratory or central nervous system).
- Children that remained longer than 10 days in the birth hospital or were hospitalized for any period over 10 days in the first three months of life.

Case definition:

A case was defined as any child that was diagnosed with one of the neurologic or renal conditions, listed in the annex. No distinction was made on whether a diagnosis was made in the clinic or hospital setting.

Exposure assessment:

Age-related cumulative exposure levels were derived from the automated data at 1 and 3 months of age.

Confounders and Effect Modifiers:

The following variables were included in the analyses: HMO site, year and month of birth, gender.

Statistical analysis:

We used proportional hazards models for all risk analyses, stratified by site, year and month of birth and adjusted for gender.

The startpoint was the date of birth or Jan 1st 95 for children born into NCK before this date (no OPD data available).

The endpoint was defined as the first of the following dates:

- the date of first diagnosis
- the first date that a child stopped being enrolled in the HMO
- December 31st, 97

The diagnoses were analyzed grouped in categories (neurologic developmental and renal) and individually if we encountered at least 50 cases. Because of the low number of cases, the heterogeneity of disorders or lack of specificity of the ICD9 codes (unspecified, other ...) we did not pursue analyses of the "degenerative neurologic" and "other neurologic" categories as a group, but only for the following diagnoses: epilepsy, acquired obstructive hydrocephalus and infantile cerebral palsy.

A separate analysis was done for premature infants with birthweight between 1500 and 2500 grams as this group was found to have certain vaccination characteristics (total number of vaccines in the first year of life, use of Hepatitis B vaccine) similar to the general population. By limiting to this group, we intended to avoid the bias by indication problem of less exposure (vaccination) in the group at higher risk of disease and thus to evaluate the protective effect of the exposure.

As some diagnoses are often made in the clinic setting, we included all four HICD codes for additional analyses of autism, sleep disorders, specific developmental and speech disorders, and epilepsy. To evaluate the influence of excluding the children with congenital or perinatal conditions, we also did the analyses for the category of neurologic developmental disorders and the speech delay for ALL infants.

We analyzed the cumulative exposure at 1 and 3 months of age. At each age we identified a maximum number of exposure categories with large enough number of children and comparable size. We then used the lowest category as referent. At 1 month we were only able to identify two categories for the rare disorders or three categories for common disorders. At three months we identified five categories for most disorders and seven categories for the three most common disorders.

Sample Size and Power:

The number of cases for the individual diagnoses varied from 1 to 1381. To achieve a relative risk (RR) of at least 2, we restricted the analyses of the individual diagnoses to those with at least 50 children.

Results:• Number of eligible children:

| | |
|---|-----------|
| All children in VSD (cycle 6) | 2,226,907 |
| Born after December 31 st 1991 | 701,307 |
| Born into GHC or NCK | 211,693 |
| Continuously enrolled first year | 121,441 |
| Received more than 1 polio in first year | 116,867 |
| Not premature | 111,239 |
| Mother did not receive HepB Ig | 111,047 |
| Excluding congenital and perinatal problems | 75,659 |
| Stay in birth- or other hospital <10 days | 75,540 |

• Number of cases identified: see attached table 2

This table gives for each category of conditions and the individual disorders, the total number of cases, the number of cases remaining after removing children with congenital or perinatal problems, the median age at the time of first diagnosis, the distribution over the two sites, the sex ratio, the distribution by year of birth and the percentage among the non-excluded that are premature.

• Risk assessment:

- At 1 month: see attached table 3

This table provides the relative risk estimates and their 95% CI for those disorders with sufficient sample size (50 cases)

- At 3 months: see attached graphs 1 to 14

These graphs illustrate the relative risks for each of the 5 or 7 categories of cumulative mercury exposure at three months of age and their 95% CIs for those disorders or categories of disorders with sufficient sample size (50 cases). Note that the Y axis can be on a linear or logarithmic scale, depending on the magnitude of the CIs.

Premature children (> 1500g):

We were able to perform this analysis only for the entire category of neurologic developmental disorders. We did not exclude children with congenital or perinatal disorders as this would reduce the number of cases to below 50.

At 1 month of age, we found a RR of 0.89 (0.62, 1.28) and 1.42 (0.62, 3.28) for exposure of 12.5 and > 12.5 μg , respectively, with 0 μg as referent.

At three months: see graph 15

For all four HMOs:

For autism and the entire category of developmental delays, the relative risks found were slightly altered: see graphs 16 and 17. For the other disorders with significant numbers of cases in the two added HMOs (sleep disorders, speech disorders, epilepsy), the results were similar to those for NCK and GHC separately.

For ALL children in all four HMOs:

For the entire category of neurologic developmental delays none of the exposure groups had an increased risk (see graph 18).

For the specific group of speech delays, the relative risk did not differ from those found for the subgroup included in the above analyses (see graph 19).

Discussion:

We focussed our analyses on the cumulative exposure levels at one and three months of age because as this age the central nervous system is still immature and more susceptible to mercury. Another reason for this focus was to minimize the difference between the dose given and the dose actually accumulated in the body. The half-life of methylmercury is estimated to be 45 days. If ethylmercury has a similar half-life, the dose given will not differ much from the dose accumulated at one and three months, given that most vaccines are given in the second and third month. In addition, the highest proportion of children in our cohort exceeded the EPA limits at one and three months of age (see study protocol). Whereas the exposure at three months of age is related to later exposure (children in high exposure groups will remain in high exposure groups at 6 or 12 months of age), this is not the case for exposure at one month of age. The main disadvantage

with the 3 months categories is the small number of cases in the lowest groups, particularly the 0 exposure group, which forced us to define the referent group as the category below 37.5 µg, except for the more common disorders.

As for the exposure evaluated at 1 month of age, which is basically an evaluation of the neonatal hepatitis B dose, we have found a significant relationship to the outcome only for **misery and unhappiness disorder** (ICD9 code 313.1). We were not able to produce a graph for the RRs at 3 months of this condition as no or few cases occur in the two lower categories. The relative risk for this condition was significantly increased (2.04, 95%CI: 1.09-3.82) when comparing those with a cumulative exposure above 62.5 µg at three months compared to those with cumulative exposure equal to or less than 62.5 µg. There is a nearly significant increased risk for the category exceeding 12.5 µg at 1 month for **attention deficit disorder**. This group includes children that received 2 doses of HepB or their first dose of Hib or DTP in the first month of life. At three months, this positive relationship is no longer significant for any category.

As for the exposure evaluated at 3 months of age, we found increasing risks of **neurologic developmental disorders** with increasing cumulative exposure to thimerosal. Within the group of developmental disorders, similar, though not statistically significant increases were seen for the sub-group called **specific delays** (ICD9 code 315) and within this sub-group for the specific disorder **developmental speech disorder** (dyslalia, ICD9 code 315.39), and for **autism** (ICD9 code 299.0), **stuttering** (ICD9 code 307.0) and **attention deficit disorder** (ICD9 code 314.0). This increase, when comparing each category of exposure to the lowest exposure group was significant only for the entire category of developmental disorders. For specific delays and speech disorder this increase occurs only above 25 µg.

As some of the above disorders are correlated (see table 1) we analyzed the RRs for each while excluding children with any of the other disorders and found similar results to the unconditional analyses.

Table 1. Number of common cases in some disorders

| | 2990 | 3070 | 3140 | 31539 |
|-------|------|------|------|-------|
| 2990 | 66 | 0 | 7 | 23 |
| 3070 | | 59 | 2 | 15 |
| 3140 | | | 158 | 20 |
| 31539 | | | | 830 |

For other disorders, the trend of the risk with increasing exposure to thimerosal was either decreasing (renal disorders) or unclear (somnambulism, mixed emotional disturbances and cerebral palsy). For epilepsy we found a significant drop of the risk when exceeding 25 μg , followed by an increasing trend. We plan to evaluate the role of earlier diagnosed convulsions in these children to better understand this finding.

To evaluate potential confounding by health care use (to identify potential sick children that may have been more likely to have the disorder and less likely to be vaccinated or, inversely, to identify those parents that bring their children in for minor ailments and are more likely to have their children vaccinated), we evaluated for each exposure level, the number of hospital and clinic diagnoses, the maximum length of hospital stay preceding the exposure and the length of stay in the birth hospital. We did not see any differences in the frequency distribution of any of these, suggesting that the categories are comparable in terms of pre-existing illnesses or health care seeking behavior of the parents.

We also looked at the number of vaccinations (DTP, Hib, HepB and complete vaccination schedule (3 Hib, 3 DTP and 2 Polio, with or without the Hepatitis B requirement)) by the end of the first year of life. The frequency distribution of these differed for the lowest exposure category, but was similar above 25 μg at three months (except for HepB). This suggests that children in the lowest exposure categories get an incomplete vaccination schedule for reasons not related to health care seeking behavior. The difference between the higher exposure categories lies in the use of Hepatitis B

vaccine, thimerosal free vaccines, combination vaccine of Hib and DTP or simply timing of the vaccinations. We plan to repeat the analyses stratified by one of the measures of health care seeking behavior and up-to-dateness of immunizations.

As for premature children, we found no associated risk of neurologic developmental outcomes to cumulative thimerosal exposure at one or three months. As we did exclude children with congenital or perinatal problems, however, this analysis is likely to be biased. When including all premature children, irrespective of their birthweight, we found a protective effect of thimerosal above the 25 µg level at three months, such as an avoidance of vaccination in the most severe group (which is also more likely to be the outcome). This is confirmed when comparing the levels of vaccination to the birthweight groups.

When including the children from all HMOs, we noticed that the increased risk of developmental neurologic disorders was no longer significant. The two added HMOs have either no outpatient data (SCK) or only since 1996 (NWK) and many of the disorders in this category (emotional disturbances, attention deficit disorder, tic disorder, and stammering) had no or very few cases in these HMOs, which may explain this finding. The curve for autism, slightly differs as most added exposed cases are found in the highest exposure categories. As mentioned before, for the other disorders the results were similar to those for the analyses of the two original HMOs (NCK and GHG).

When including the children with congenital or perinatal conditions, no increase was found for the broad categories of any or specific developmental delays. This suggests an avoidance of immunization in infants at highest risk of developing these conditions. For the specific diagnosis of speech delay this phenomenon did not occur.

In conclusion, we can state that this analysis does not rule out that receipt of thimerosal containing vaccine in children under three months of age may be related to an increased risk of neurologic developmental disorders. Specific conditions that may warrant a detailed study include autism, dyslalia, misery and unhappiness disorder and attention deficit disorder. There is no indication that thimerosal exposure is linked to an increased risk of degenerative or other non-developmental neurologic disorders or renal disease.

Limitations:

- We have limited our analyses to a list of potential outcomes based on prior knowledge of adverse conditions found in infants exposed to high doses of methylmercury. We cannot rule out other disorders potentially related to exposure to ethylmercury.
- We were able to evaluate only relatively severe conditions that come to medical attention, and not possibly more subtle effects that would require neuropsychological testing.
- The study was underpowered for some conditions, particularly the renal outcomes.
- Some misclassification errors may have occurred in the exposure assessment (some vaccinations, particularly the neonatal HepB dose may not have been reported).
- We were not able to differentiate between single dose thimerosal free Hib vaccines and multi-dose thimerosal containing Hib vaccines. The analyses were done assuming all vaccines to come from multi-dose vials. An analysis assuming all Hib vaccines to come from single dose-vials did not substantially alter the results.
- We had no information on some potential confounders, such as maternal smoking or fish consumption.
- We could not differentiate between the difference in effect from the preservative or active component in the vaccines. Exposure to thimerosal from vaccines is invariably linked to the likelihood of being vaccinated with Hepatitis B, DTP or Hib.
- We relied entirely on automated data and did not control its quality. This is assumed to be high for most data, but maybe less so for birthweight and/or gestational age.

Proposal for future study

As we do not expect to gain substantially more or different information from verification of the current findings through chart abstractions or case-control study, we propose to conduct a follow-up study of current of the neuropsychologic functioning of cohorts children randomly drawn from different exposure categories.

Table 2. Number of children identified per disorder and distribution by site, gender, year of birth and prematurity

| Code | Description | Total | Not excl † | Asian Age * | Site (%) | | Sex (%) | | Year of birth (%) | | | | | % Prem |
|--|-------------------------------------|--------|---------------|----------------|----------|-----|---------|----|-------------------|----|----|----|----|--------|
| | | | | | C | W | f | m | 92 | 93 | 94 | 95 | 96 | |
| ALL kids | | 116229 | 76509 | | 82 | 18 | 50 | 50 | 17 | 21 | 19 | 19 | 22 | 2 |
| Neurologic degenerative disorders: | | 145 | 57 | 22 | 67 | 33 | 33 | 37 | 21 | 19 | 33 | 7 | 12 | 0 |
| 330.x | Cerebral degenerations usually | 7 | 4 | 17 | 75 | 25 | 50 | 50 | 25 | 25 | 0 | 0 | 50 | 0 |
| 331.x | Other cerebral degenerative disease | 59 | 14 | 16 | 64 | 36 | 43 | 57 | 14 | 29 | 29 | 7 | 21 | 0 |
| 333.x | Other extrapyramidal disease and | 47 | 28 | 28 | 64 | 36 | 29 | 71 | 29 | 18 | 29 | 4 | 11 | 0 |
| 334.x | Spinocerebellar disease | 8 | 3 | 23 | 67 | 33 | 33 | 67 | 33 | 0 | 33 | 33 | 0 | 0 |
| 335.x | Anterior horn cell disease | 3 | 3 | 29 | 67 | 33 | 33 | 67 | 33 | 33 | 33 | 0 | 0 | 0 |
| Neurologic developmental disabilities: | | 2991 | 1743 | 27 | 52 | 48 | 35 | 65 | 22 | 27 | 24 | 17 | 8 | 4 |
| 299.0 | Autism | 109 | 67 | 40 | 85 | 15 | 13 | 87 | 30 | 39 | 25 | 6 | 0 | 7 |
| 299.8 | Other childhood psychosis | 39 | 22 | 44 | 86 | 14 | 9 | 91 | 41 | 32 | 18 | 9 | 0 | 0 |
| 299.9 | Other unspecified psychosis | 17 | 17 | 42 | 0 | 100 | 12 | 88 | 47 | 12 | 35 | 6 | 0 | 0 |
| 307.0 | Stammering & stuttering | 80 | 59 | 39 | 45 | 55 | 32 | 68 | 24 | 37 | 34 | 5 | 0 | 0 |
| 307.2 | Tics | 70 | 43 | 36 | 53 | 47 | 40 | 60 | 35 | 23 | 19 | 16 | 7 | 0 |
| 307.3 | Repetitive movements | 2 | 2 | 20 | 0 | 100 | 50 | 50 | 50 | 0 | 50 | 0 | 0 | 0 |
| 307.4 | Sleep disorders | 121 | 81 | 26 | 53 | 47 | 41 | 59 | 10 | 32 | 21 | 21 | 16 | 1 |
| 307.5 | Eating disorders | 85 | 45 | 21 | 96 | 4 | 42 | 58 | 13 | 36 | 33 | 11 | 7 | 0 |
| 307.6 | Enuresis | 10 | 4 | 53 | 100 | 0 | 25 | 75 | 75 | 25 | 0 | 0 | 0 | 0 |
| 313 | Disturbance of emotions specific to | 214 | 150 | 24 | 25 | 75 | 43 | 57 | 32 | 30 | 21 | 9 | 5 | 1 |
| 314.0 | Attention deficit Sy | 248 | 158 | 41 | 74 | 26 | 22 | 78 | 41 | 34 | 16 | 3 | 6 | 0 |
| 315 | Specific delays in development | 2163 | 1235 | 27 | 50 | 50 | 33 | 67 | 20 | 27 | 25 | 19 | 8 | 5 |
| 315.9 | Developmental speech delay | 1240 | 833 | 32 | 56 | 44 | 29 | 71 | 20 | 30 | 29 | 18 | 4 | 2 |
| 3159 | Unspecified developmental delay | 843 | 363 | 21 | 43 | 57 | 40 | 60 | 15 | 20 | 21 | 23 | 17 | 9 |
| 317-319 | Mental retardation | 50 | 12 | 43 | 83 | 67 | 33 | 67 | 42 | 33 | 17 | 8 | 0 | 8 |
| Code | Description | Total | Not excl † | Asian Age * | Site (%) | | Sex (%) | | Year of birth (%) | | | | | % Prem |
| Other neurologic conditions: | | 687 | 256 | 23 | C | W | f | m | 92 | 93 | 94 | 95 | 96 | |
| 343.x | Infantile cerebral palsy | 289 | 61 | 22 | 77 | 23 | 41 | 59 | 21 | 13 | 30 | 23 | 11 | 7 |

Table 3. Sample size and relative risks for grouped and specific disorders, based on cumulative mercury exposure at 1 month of age

| Code | Description | Cases | RR ± 95% CI (Ref. = 0 µg) | |
|--|-------------------------------------|-------|---------------------------|-------------------|
| | | | 12.5 µg | > 12.5 µg |
| Neurologic developmental disabilities: | | | | |
| 299.0 | Autism | 1743 | 1.08 (0.96, 1.21) | 0.87 (0.60, 1.27) |
| 307.0 | Stammering & stuttering | 67 | 0.96 (0.55, 1.68) | 1.58 (0.48, 5.20) |
| 307.4 | Sleep disorders | 59 | 0.97 (0.52, 1.79) | No cases |
| 313 | Disturbance of emotions specific to | 81 | 0.77 (0.45, 1.29) | 1.74 (0.53, 5.73) |
| 313.1 | Misery and unhappiness disorder | 150 | 1.44 (0.93, 2.23) | 1.07 (0.26, 4.45) |
| 313.8 | Mixed emotional disturbances | 81 | 2.68 (1.29, 5.55) | No cases |
| 314.0 | Attention deficit Sy | 53 | 0.74 (0.38, 1.44) | 1.48 (0.35, 6.33) |
| 315 | Specific delays in development | 158 | 0.96 (0.65, 1.41) | 2.14 (0.99, 4.62) |
| 315.39 | Developmental speech delay | 1235 | 1.06 (0.92, 1.22) | 0.76 (0.47, 1.23) |
| 315.9 | Unspecified delays in development | 833 | 1.11 (0.95, 1.31) | 0.80 (0.46, 1.39) |
| Other neurologic conditions: | | | | |
| 343.x | Infantile cerebral palsy | 298 | 1.00 (0.76, 1.32) | 0.69 (0.25, 1.87) |
| 345 | Epilepsy | 256 | | |
| Renal conditions: | | | | |
| 593.9 | Unspecified disease of kidney | 61 | 0.93 (0.49, 1.76) | 0.81 (0.11, 6.05) |
| | | 123 | 1.26 (0.84, 1.87) | 0.78 (0.19, 3.21) |
| | | 99 | 0.99 (0.64, 1.52) | 0.36 (0.05, 2.65) |
| | | 56 | 1.35 (0.76, 2.40) | No cases |

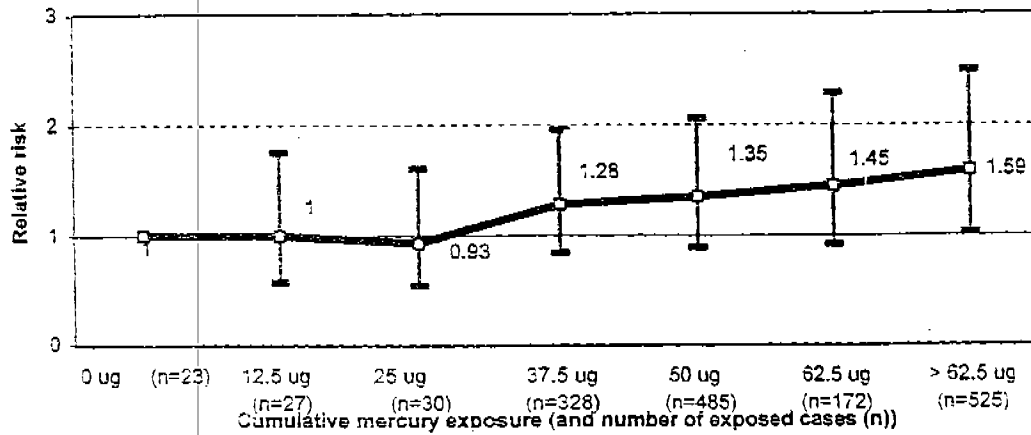
* at first diagnosis, in months

| | | | | | | | | | | | | | | |
|--------|----------------------------------|-----|-----|----|-----|-----|----|-----|-----|----|----|----|----|---|
| 345 | Epilepsy | 287 | 123 | 24 | 88 | 12 | 41 | 59 | 20 | 26 | 20 | 20 | 12 | 5 |
| 346 | Migraine | 30 | 21 | 39 | 76 | 24 | 48 | 52 | 48 | 29 | 19 | 5 | 0 | 5 |
| 348.x | Other conditions of brain | 49 | 19 | 19 | 53 | 47 | 37 | 63 | 21 | 26 | 16 | 21 | 0 | 5 |
| 349.82 | Toxic encephalopathy | 0 | | | | | | | | | | | | |
| 349.9 | Unspecified disorders of nervous | 63 | 29 | 31 | 76 | 24 | 34 | 66 | 31 | 17 | 31 | 14 | 3 | 0 |
| 356.x | Isopathic polyneuropathy | 6 | 1 | 24 | | | | | | | | | | |
| 357.x | Other polyneuropathies | 0 | | | | | | | | | | | | |
| 358.x | Toxic and other myoneural | 7 | 3 | 17 | 33 | 67 | 67 | 33 | 33 | 67 | 0 | 0 | 0 | 0 |
| 359.x | Toxic and other myopathies | 11 | 5 | 29 | 100 | 0 | 20 | 80 | 40 | 20 | 0 | 0 | 40 | 0 |
| | Renal conditions: | 194 | 99 | 22 | 84 | 16 | 48 | 52 | 23 | 22 | 19 | 19 | 15 | 3 |
| 580 | Acute glomerulonephritis | 2 | 1 | 45 | | | | | | | | | | |
| 581 | Nephrotic Sy | 17 | 13 | 30 | 100 | 0 | 31 | 69 | 46 | 15 | 8 | 23 | 8 | 0 |
| 582 | Chronic glomerulonephritis | 8 | 5 | 20 | 0 | 100 | 20 | 80 | 40 | 20 | 20 | 20 | 0 | 0 |
| 583 | Not specified as d nephropathy | 56 | 31 | 19 | 90 | 10 | 55 | 45 | 32 | 26 | 26 | 10 | 6 | 0 |
| 584 | Acute renal failure | 10 | 5 | 31 | 80 | 20 | 60 | 40 | 40 | 20 | 0 | 0 | 40 | 0 |
| 585 | Chronic renal failure | 9 | 3 | 51 | 67 | 33 | 0 | 100 | 100 | 0 | 0 | 0 | 0 | 0 |
| 586 | Unspecified renal failure | 11 | 7 | 25 | 57 | 43 | 29 | 71 | 14 | 29 | 0 | 0 | 57 | 0 |
| 593.9 | Unspecified disease of kidney | 106 | 56 | 24 | 87 | 13 | 46 | 54 | 18 | 21 | 18 | 23 | 30 | 5 |

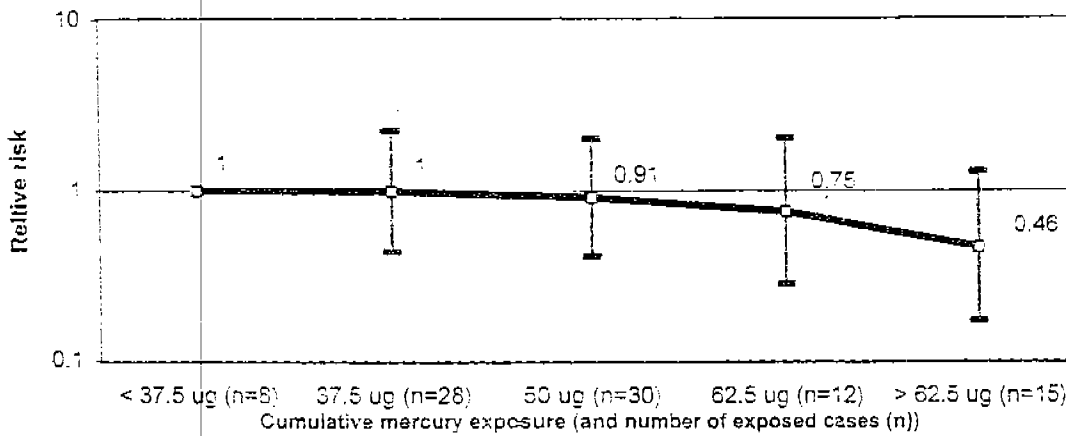
† at first diagnosis, in months

‡ The number not excluded by eliminating congenital and perinatal disorders

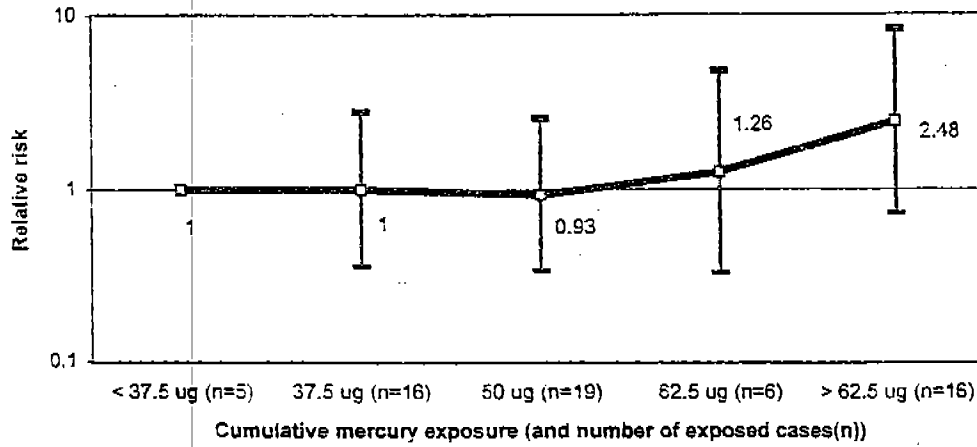
Graph 1: Relative risk + 95 % CI of Developmental neurologic disorders after different exposure levels of thimerosal at 3 months of age, NCK &GHC



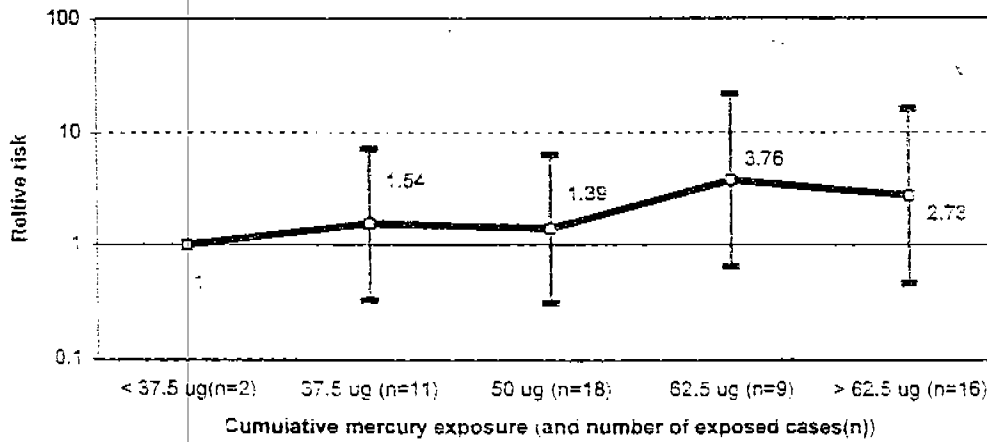
Graph 2: Relative risk + 95 % CI of Renal disorders after different exposure levels of thimerosal at 3 months of age, NCK &GHC



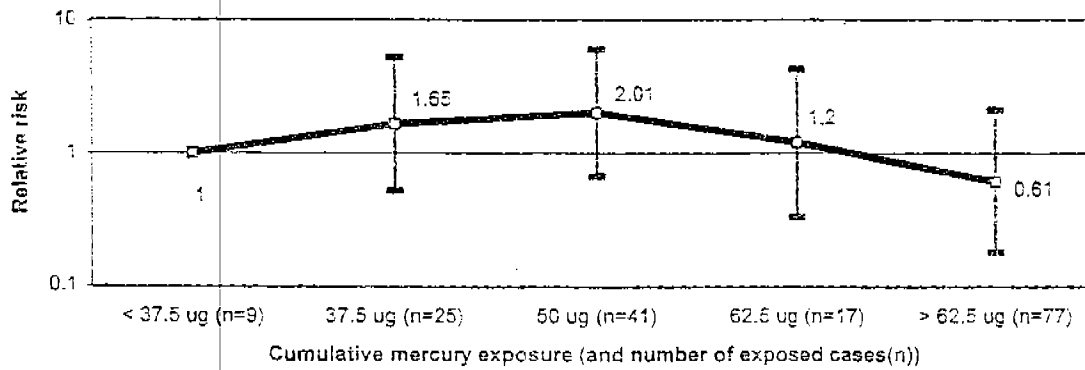
Graph 3: Relative risk + 95 % CI of Autism after different exposure levels of thimerosal at 3 months of age, NCK &GHC



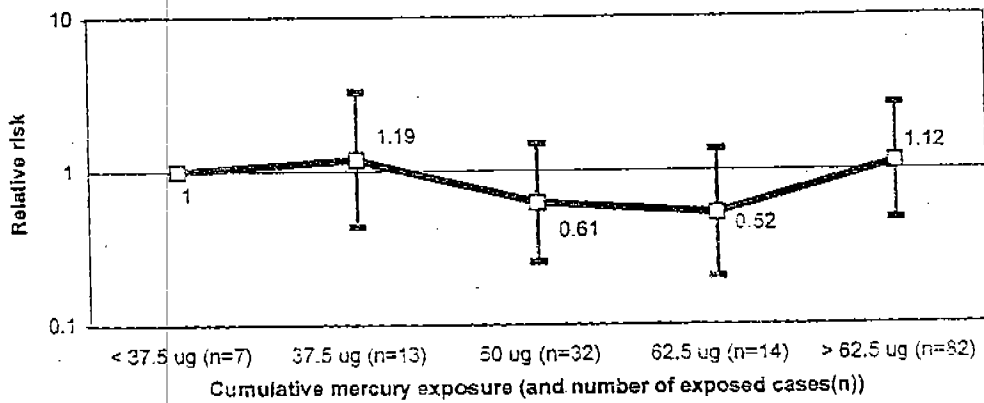
Graph 4: Relative risk + 95 % CI of Stammering after different exposure levels of thimerosal at 3 months of age, NCK &GHC



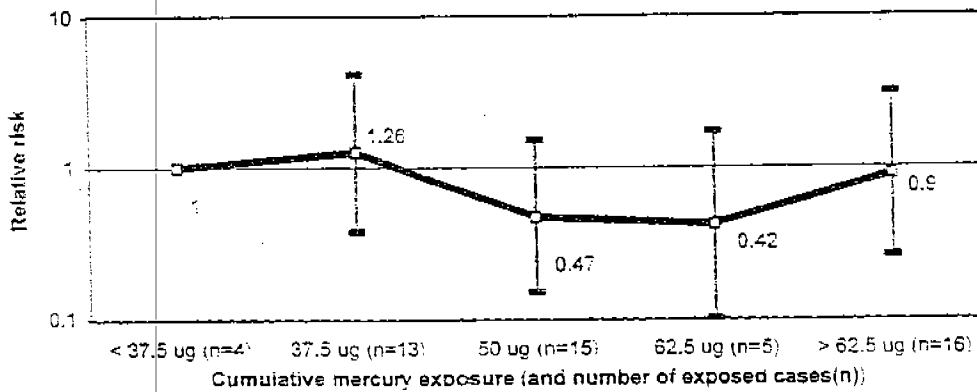
Graph 5: Relative risk + 95 % CI of Somnambulism or night terrors after different exposure levels of thimerosal at 3 months of age, NCK &GHC



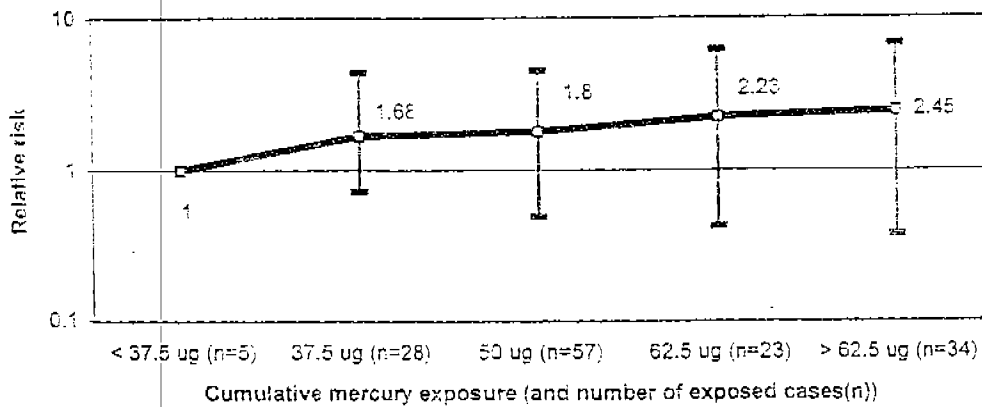
Graph 6: Relative risk + 95 % CI of Disturbance of emotions specific to childhood and adolescence after different exposure levels of thimerosal at 3 months of age, NCK &GHC



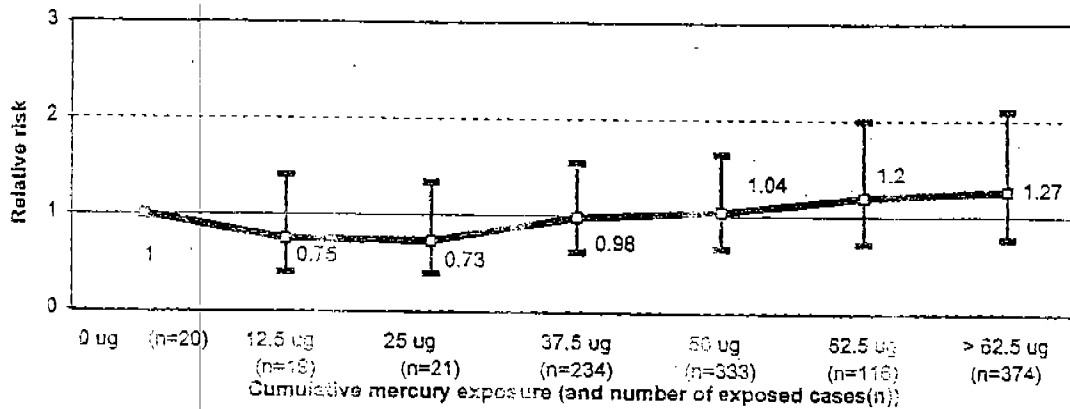
Graph 7: Relative risk + 95 % CI of Other or mixed emotional disturbances of childhood and adolescence after different exposure levels of thimerosal at 3 months of age, NCK &GHC



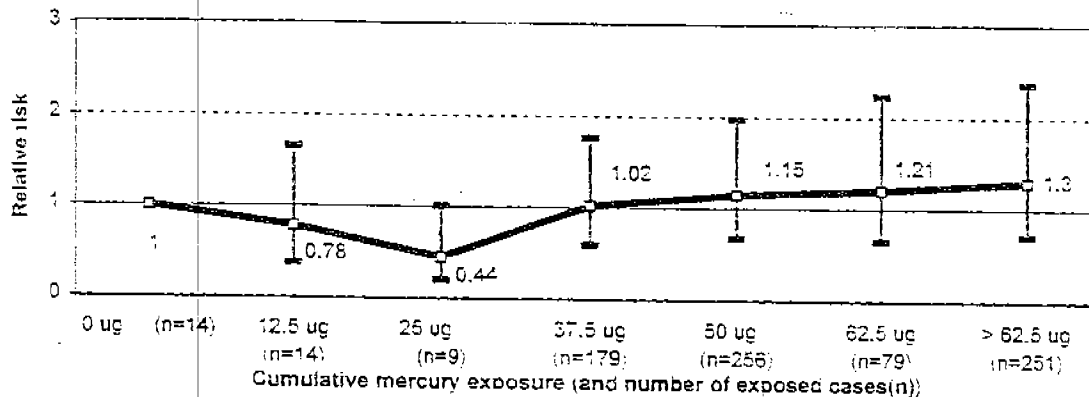
Graph 8: Relative risk + 95 % CI of Attention Deficit Disorder after different exposure levels of thimerosal at 3 months of age, NCK &GHC



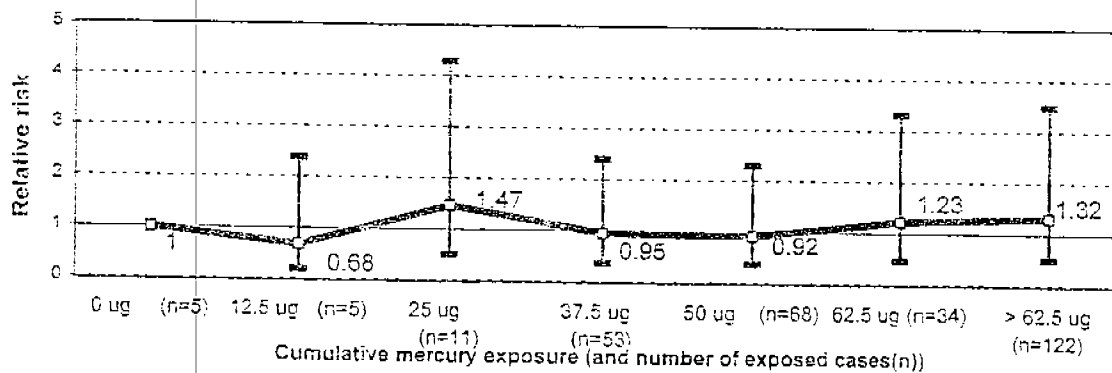
Graph 9: Relative risk + 95 % CI of Specific delays in development after different exposure levels of thimerosal at 3 months of age, NCK &GHC



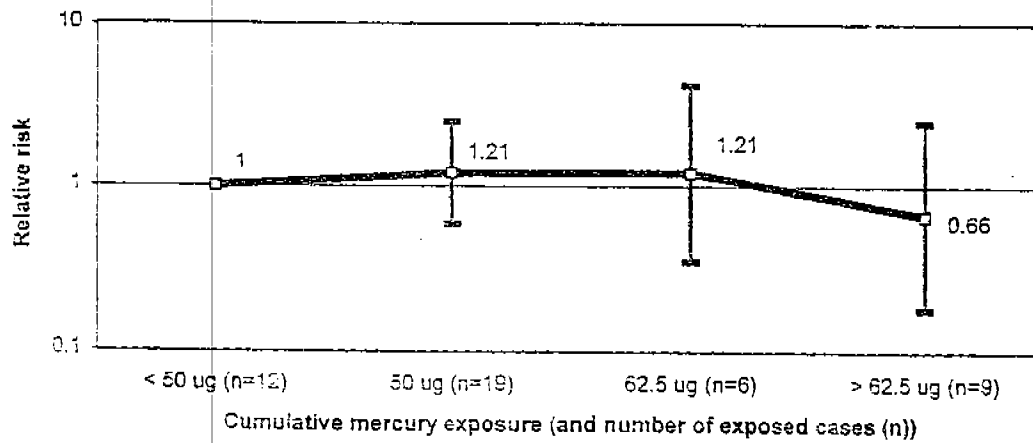
Graph 10: Relative risk + 95 % CI of Developmental speech disorder after different exposure levels of thimerosal at 3 months of age, NCK &GHC



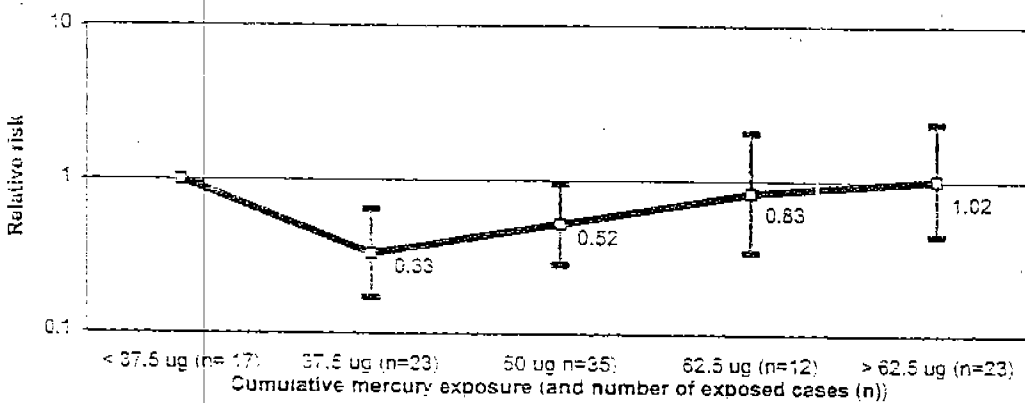
Graph 11: Relative risk + 95 % CI of Unspecified delay in development after different exposure levels of thimerosal at 3 months of age, NCK &GHC



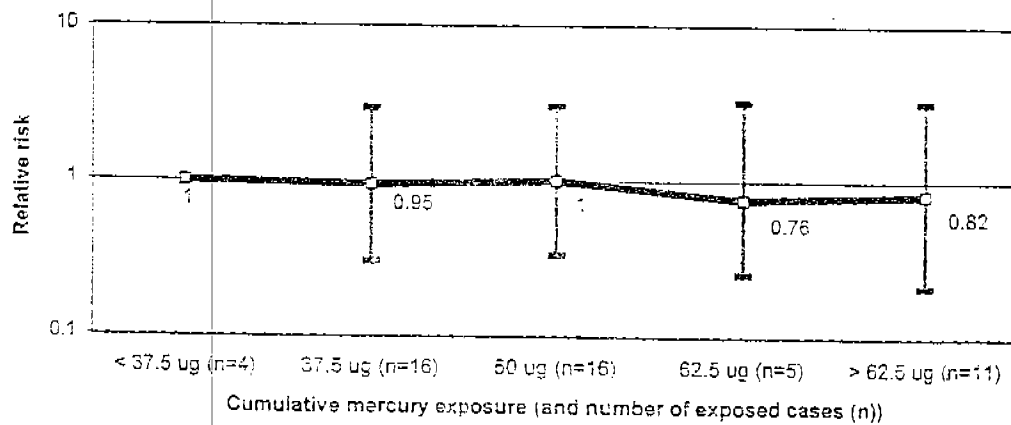
Graph 12: Relative risk + 95 % CI of Infantile cerebral palsy after different exposure levels of thimerosal at 3 months of age, NCK &GHC



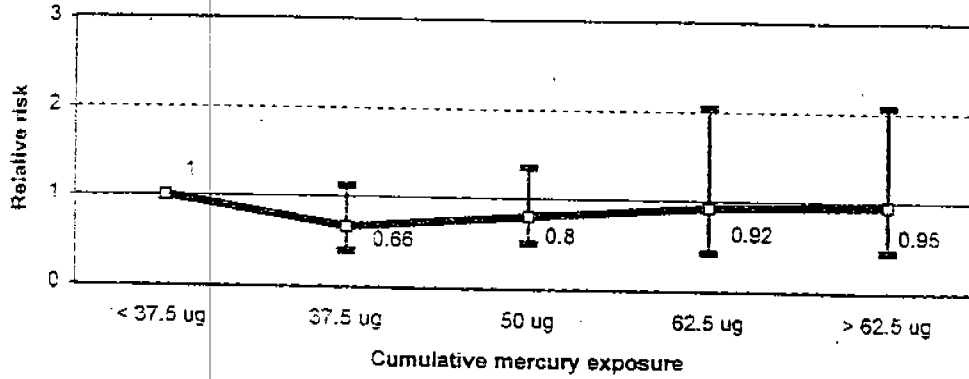
Graph 13: Relative risk + 95 % CI of Epilepsy after different exposure levels of thimerosal at 3 months of age, NCK &GHC



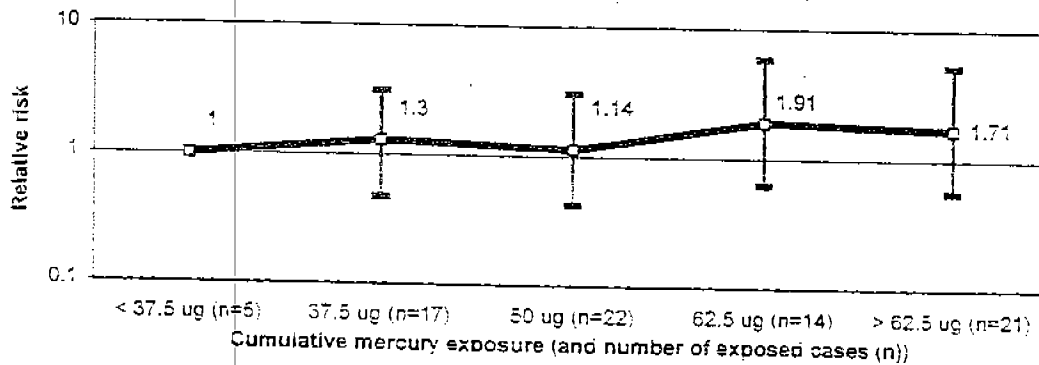
Graph 14: Relative risk + 95 % CI of Unspecified kidney or ureter disorder after different exposure levels of thimerosal at 3 months of age, NCK &GHC



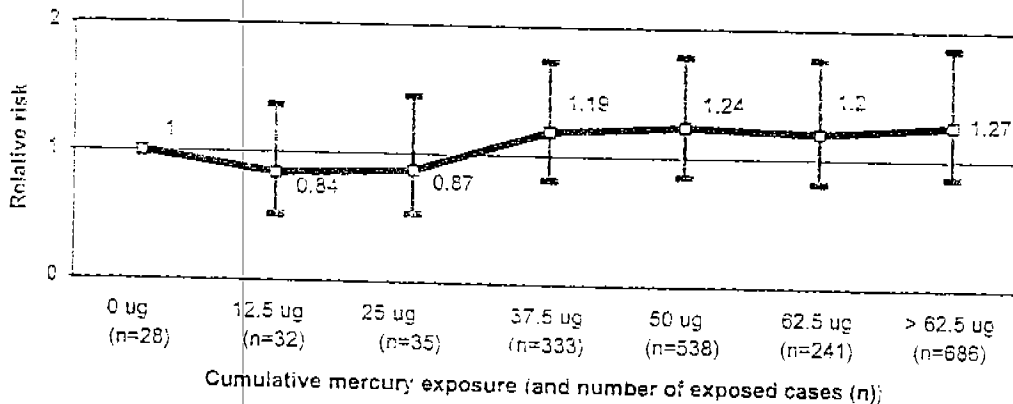
Graph 15: Relative risk + 95 % CI of Developmental neurologic disorders among prematures (>1500 g) after different exposure levels of thimerosal at 3 months of age



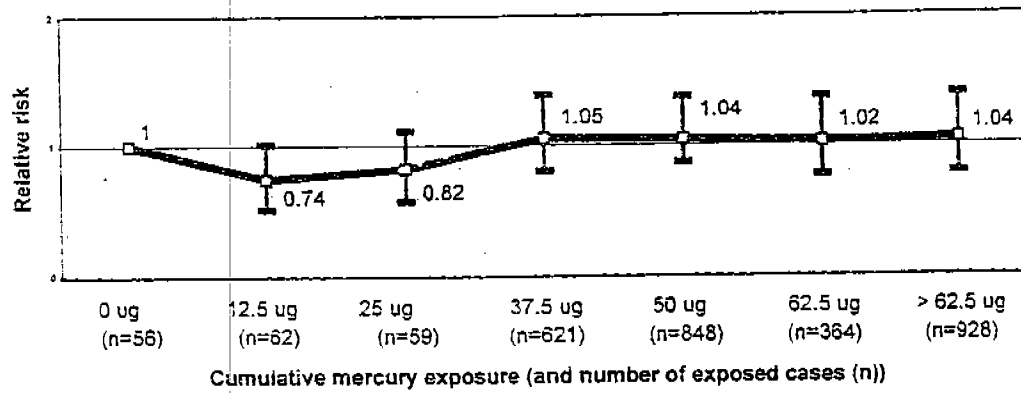
Graph 16: Relative risk + 95 % CI of Autism after different exposure levels of thimerosal at 3 months of age for all HMOs



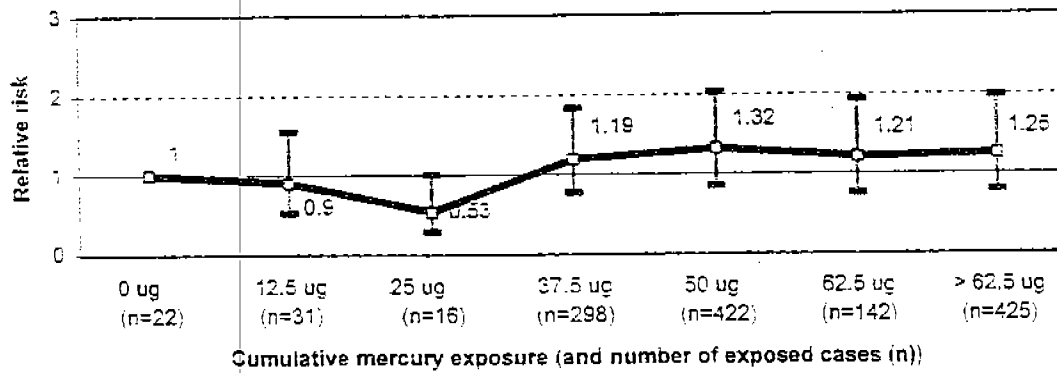
Graph 17: Relative risk + 95 % CI of Developmental neurologic disorders after different exposure levels of thimerosal at 3 months of age for all HMOs



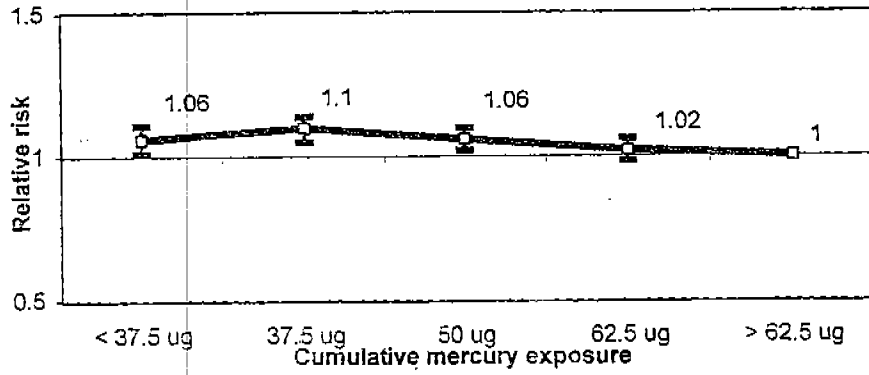
Graph 18: Relative risk + 95 % CI of Developmental neurologic disorders after different exposure levels of thimerosal at 3 months of age for ALL kids, all HMOs



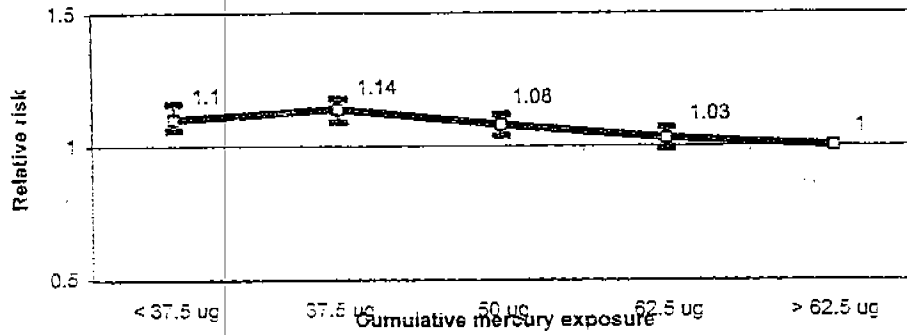
Graph 19: Relative risk + 95 % CI of Developmental speech disorder after different exposure levels of thimerosal at 3 months of age for ALL kids, all HMOs



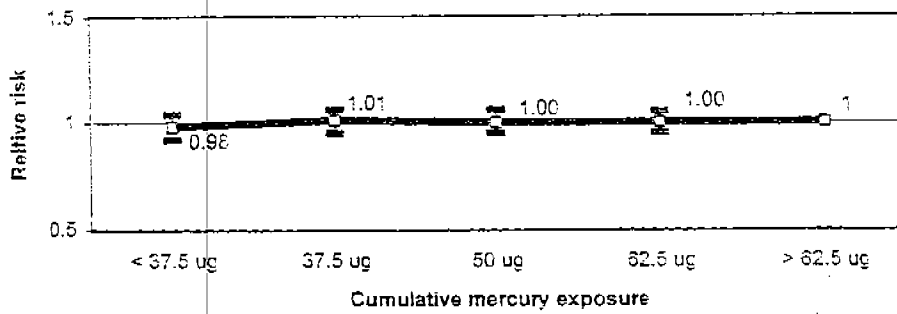
Unspecified otitis media



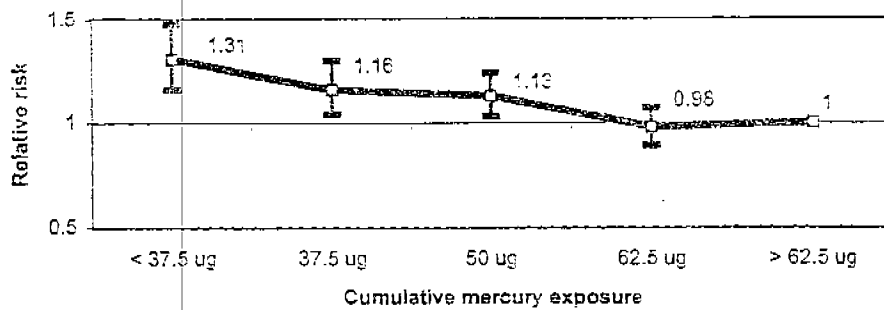
Acute URI - NOS



Non specific non-infectious Gastro-enteritis



Unspecified injury



Vaccine combinations in the cumulative mercury exposure categories at three months of age:

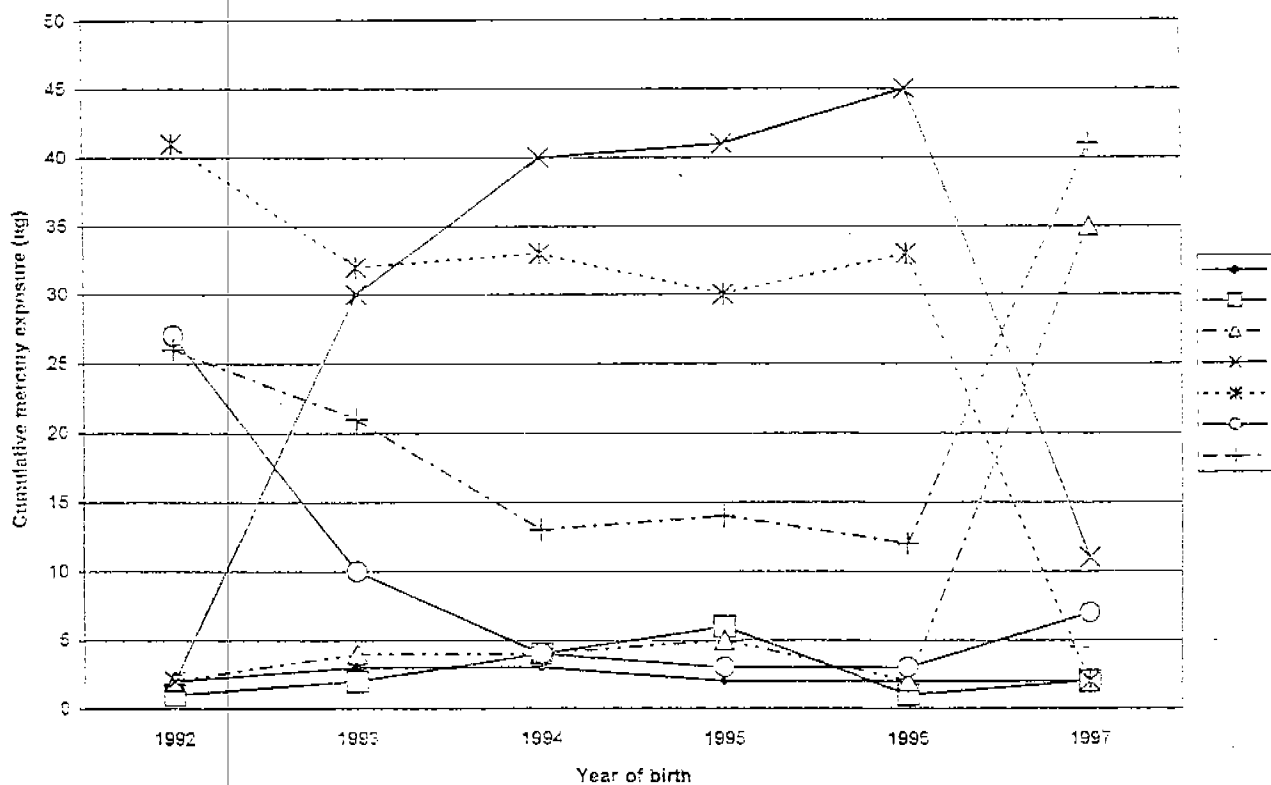
| Category | Frequency | Combinations |
|-----------|--------------------|--|
| 0 µg | 2% | No vaccines |
| 12.5 µg | 2% | 1 HepB only |
| 25 µg | 4% | 2 HepB, 0 DTP, 0 Hib (25%) 1 HepB - Hib, 1 DTP (25%) 0 HepB, 1 DTP-Hib (50%) |
| 37.5 µg | 31% | 1 HepB, 1 DTP-Hib |
| 50 µg | 32% | 2 HepB, 1 DTP-Hib (75%) 0 HepB, 1 DTP, 1 Hib (25%) |
| 62.5 µg | 9% | 1 HepB, 1 DTP, 1 Hib |
| > 62.5 µg | 18% (0.3% > 75 µg) | 2 HepB, 1 DTP, 1 Hib |

Note: DTP includes DTaP

Mercury contents (µg) HepB: 12.5, DTP(DTaP): 25, Hib: 25*, DTP-Hib: 25, HepB-Hib: 0

*: we assumed all Hib to be from multi-dose vials (thimerosal containing)

Frequency of categories of cumulative mercury exposure at three months of age, by birthyear



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Thimerosal VSD study- Follow-up on conference call 03/02/2000

This report summarizes additional analyses I did as a result of the many suggestions received during the mentioned conference call.

As the outcome "neurologic developmental disorders" seems to provide a reasonable summary of all important outcomes (in terms of sample size), I have restricted the following analyses to this category of outcomes.

Also for sake of reducing the number of analyses, and to keep the results easier to interpret, I have used the cumulative exposure at three months as a continuous variable. This also resolves the problem of which reference category to choose.

This follow-up report addresses the following issues:

- Ascertainment of birth dose HepB
- Socio-economic status
- Health care seeking behavior:
- Adjustment for age
- Data from NCK before 1995

The following are responses to correspondence after the conference call

- Control diagnoses
- Comparison to number of vaccines, aluminum
- Thimerosal content of Hib vaccines

1. Ascertainment of birth dose HepB

On a request by Bob Davis to give an idea on the accuracy of the birth dose for HepB in the automated data, NCK estimated the capture of the birth dose to be in the high 90% range from 7/91 onwards. GHC also expressed confidence in their capture of the birth dose from 10/92 onwards.

I tried to estimate the proportion of missed birth doses, assuming that these were missed if the automated data suggested that a child, continuously enrolled in the first two years, had had only two doses of Hepatitis B by the age of 2 years, but all the four DTP and Hib and three polio vaccinations. This approach suggested that the birth dose was not registered in 3.8% and 16.5% at NCK and GHC respectively

Alternatively, I looked at children continuously enrolled in the first year that had only 1 dose of HepB by six months, but were on schedule for DTP, Hib and Polio (at least two of each). According to this analysis, 4.2 % and 17.9% of birth doses are missed at NCK and GHC respectively. Over the years there is a steady improvement at NCK from 5.9%

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to 3.3%, whereas at GHC, there is an improvement after an initial decline (11.8%, 22.3%, 25.9%, 15.6% and 13.6% for '92, '93, '94, '95, and '96 respectively).

These data are comparable to findings in John Mullooly's paper on data quality. Although these rates are relatively high at GHC, they probably have little effect on the thimerosal analysis as only 12.5 µg of ethylmercury to the cumulative dose is added for each HepB vaccine.

2. Socio-economic status

I linked the files to 1990 census data on blocks of homes. I then assigned race and income to the children according to which was the most prevalent in their block (e.g. if 60% was white, 30% black, 5% asian etc, I would call the child white). Doing this I obtained the following distribution of race and income;

- Race:

White 83%

Hispanic 6.9%

Asian 6.5%

Black 3.7%

Native American 0.0%

- Yearly household income:

Under 15 K: 6.8 %

15 - 24 K: 1.1 %

25 - 49 K: 66.9 %

50- 74 K: 10.8 %

75 K: 14.3 %

I found no association between the level of income and Hg exposure levels (at three months). Although there was a slight increase of exposure among whites and Asians (average Hg exposure at 3 months 50 µg and 49 µg vs. 46 µg and 47 µg among blacks and Hispanics) and an increased chance of the outcome among whites, stratification by race or income did not change the RR estimates.

3. HC seeking behavior: well child clinics (ICD9 codes V200, V201 and V202): these seem to be rarely recorded in both HMOs. For those approximately 10% of children in which it is recorded, there was no difference across the strata of exposure in the number of well child visits

4. Adjustment for age (Check of proportionality assumption)

As age is equal to time in the PH model, adjusting for age is equivalent to checking the proportionality. In a stratified model one needs to check the assumption in the strata. Since the model uses over 100 strata, it would be impossible however to check this

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formally for every stratum. As an alternative I did subanalyses for the different years of age at which a child was right censored because of either diagnosis or stopped enrollment.

For all ages this gives: RR 1.006 (1.004, 1.010)

Under 1 year: 1.006 (0.985, 1.027)

1 - 2 years: 1.010 (1.000, 1.020)

2 - 3 years: 1.007 (0.999, 1.014)

3 - 4 years: 1.009 (0.999, 1.019)

> 4 years: 1.002 (0.990, 1.014)

There appears to be a decline in the RR after 4 years of age, but a rather constant RR before that.

As an alternative to the PH model, I also ran a logistic regression model, including gender, site, year and month of birth as covariates, exposure measure and outcome as in the PH model, imposing a minimum age of continuous enrollment for non-cases (imposing the same minimal age of diagnosis on cases removed too many of them and the model would not converge).

The RR thus obtained was

1.007 (1.002, 1.011) for no minimal time of enrollment

1.009 (1.004, 1.014) for minimal 3 years of enrollment

1.008 (1.001, 1.014) for minimal 4 years of enrollment

I conclude that the PH model does not depend on age (at least by years) and that the proportionality assumption is valid.

5. Data from NCK before 1995:

The NCK group is currently checking for a sample of the cases of speech disorder (ICD9 31539) on the date of diagnosis.

6. Control diagnoses

I looked at the relationship between the exposure and a number of frequent outcomes for which one would not expect a relationship to exist:

- Unspecified conjunctivitis
- Nonspecified, noninfectious diarrhea
- Unspecified injury

For the first two there was no trend of increased/decreased risk with increasing (thimerosal) exposure. For injury the exposure shows a significant protective effect (RR decreases .3% per μg of additional cumulative mercury exposure at three months). The relative risks for the different exposure categories are attached in Graph 1.

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7. Comparison to number of vaccines, aluminum

The purpose of these analyses would be to differentiate between the effect of thimerosal and the vaccines themselves. Unfortunately (nearly) all vaccines in our analysis were either thimerosal containing (DTP, DTaP HepB and Hib) or thimerosal free (polio). Any analysis of the number of vaccines or aluminum as an exposure variable would show a correlation to the thimerosal analysis and not be helpful in the distinction. I ran analyses with the number of Hib, DTP, HepB and polio vaccines as exposure and found a relationship of the risk to the number of DTP and Hib vaccines received at three months, which was to be expected. I also found a relationship to the age at which the first Hib vaccine was given (the later the vaccine given, the less chance of neurologic developmental delay), which was also to be expected. Surprisingly, I did not find this for DTP.

To easily differentiate between the effect of thimerosal and vaccine, we would need to compare a group that received thimerosal free vaccine to thimerosal containing vaccine, which leads to point 8. The closest we have come to such a comparison was by comparing the group that received the DTP-Hib combination vaccine (containing 25 µg of mercury) to the group that received the DTP and Hib separately (each 25 µg of mercury). This comparison showed no significant relation to the outcome neurologic developmental delay.

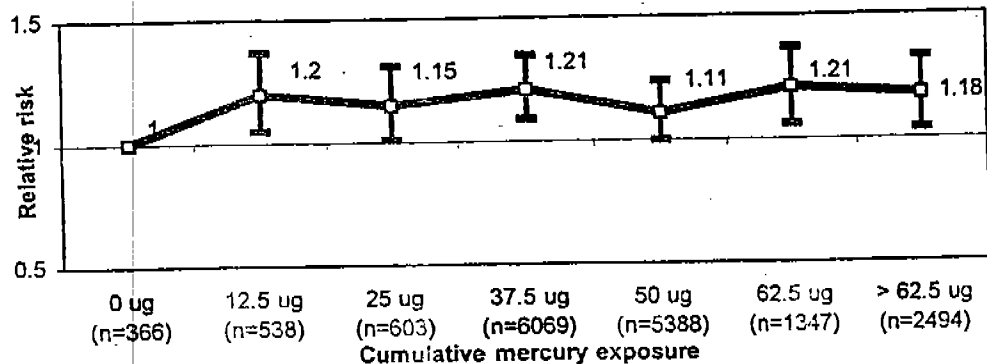
8. Thimerosal content of Hib vaccines:

The FDA is currently matching the lot numbers to information on the exact or mean thimerosal content for all vaccines used in the two HMOs.

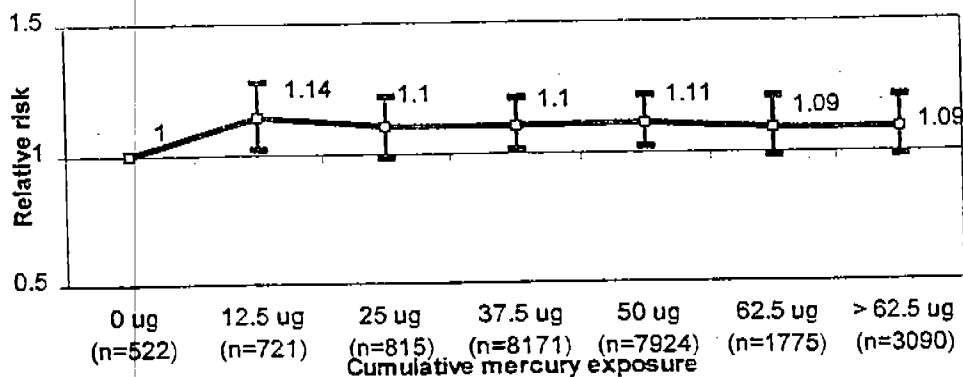
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Graph 1. Relative risk + 95 % confidence intervals of after different exposure levels of thimerosal at 3 months of age for some additional conditions

Unspecified conjunctivitis



Non specific non-infectious Gastro-enteritis



Unspecified injury

